

STREPTOMYCIN SENSITIZATION*

BY

DAVID C. HUTFIELD

Department of Venereal Diseases, St. Mary's Hospital, London, W.2

The Committee on Safety of Drugs, set up under the chairmanship of Sir Derrick Dunlop for the purpose of investigating adverse reactions to drugs, has asked medical practitioners to report adverse reactions to drugs administered by them, so that a register may be compiled in order to establish an "early warning system". This is designed to give prompt advice to practitioners, if it is found that the frequency or seriousness of reactions to a particular drug constitutes a hazard to patients.

Venereologists are especially well situated to study adverse reactions to antibiotic and chemotherapeutic drugs, since these are frequently used in departments of venereal diseases. Some clinics have, in fact, already responded to the task of supplying the information required for the establishment of the "register".

Most antibiotics produce an adverse reaction at some time or other. On rare occasions the reaction may result in death, but usually it is completely reversible once the administration of the drug has been stopped. Streptomycin, however, is an exception, since one of its neurotoxic effects (*i.e.* eighth nerve damage) may be permanent, even if the initial dose has been small and in some cases it may occur after the drug has been stopped (Ranger, 1959).

Adverse reactions to streptomycin can conveniently be divided into two groups, allergic and toxic; these can be subdivided again according to symptoms and signs and classified as follows:

(A) Allergic

(1) *Anaphylaxis*.—This can occur within a few hours of injection and is usually reversible but may be fatal. Symptoms and signs are those of shock associated with a fall in blood pressure, dyspnoea, cyanosis, and collapse. Urticaria and angio-oedema may also occur (Criepe, 1950).

(2) *Serum Sickness*.—Symptoms and signs may be delayed several days after the injection and take the form of malaise, a rise in body temperature, rigors, arthralgia,

maculopapular rash, conjunctival injection, lymphadenopathy, and eosinophilia (Criepe, 1950).

(3) *Atopy*.—Single injections may precipitate attacks of asthma (Smith and Zirk, 1961) and hay fever (Criepe, 1950).

(4) *Local Irritation*.—The site of injection and topical applications may act as a focus of irritation (Riches, 1954a).

(B) Toxic

(1) *Neurological*

- (a) Damage to the eighth nerve involving both auditory and vestibular components, resulting in symptoms and signs of deafness and vertigo, frequently occurs (Ranger, 1959).
- (b) Peripheral neuritis. Circum-oral paraesthesiae (Doyle, 1960) and difficulty in visual accommodation are common manifestations (Riches, 1954a).

(2) *Cephalic*

- (a) Headache, lassitude, nervousness and insomnia may be associated with multiple injections (Riches, 1954a; Fein, 1959).
- (b) Various psychotic and euphoric states have been described by Kalinowski (1960) and Chakravarty and Sircar (1961) respectively.
- (c) Encephalopathy and encephalomeningitis have been described by Ranger (1959).

(3) *Dermatological*.—Various allergic and toxic skin eruptions may be associated with the use of this drug.

- (a) Maculopapular rash (Criepe, 1950).
- (b) Contact eczema (Sandler, 1955).
- (c) Exfoliative dermatitis (Ranger, 1959)
- (d) Pityriasis rosea (Fein, 1959).

(4) *Gastro-intestinal*.—Nausea, vomiting, and diarrhoea are characteristic side-effects (Fein, 1959).

(5) *Haematological*.—Various toxic and allergic blood dyscrasias resulting from the use of this drug have been described.

- (a) Anaemia (Fein, 1959).
- (b) Granulocytopenia (Fein, 1959).
- (c) Eosinophilia (Criepe, 1950; Chakravarty and Sircar, 1961).

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(6) *Hepatic*.—Presenting with symptoms and signs of jaundice (Fein, 1959; Kalinowski, 1960).

(7) *Renal*.—Presenting with symptoms and signs of impaired renal function as a result of renal irritation. (Riches, 1954a).

(8) *Arthritic*.—A rheumatoid type of arthritis occurring as a complication from the continued use of this drug has been described by Fein (1959).

The incidence of adverse reactions to streptomycin has been reported to range from 5·9 to 36 per cent. of patients treated:

5·9 per cent. of	707 patients	(Aamodt, 1959)
10·9 per cent. of	510 patients	(Chakravarty and Sircar, 1961).
7·5 per cent. of	156 patients	(Smith, 1960).
8·3 per cent. of	3,017 patients	(Kalinowski, 1960).

Smith and Zirk (1961) stated that allergic reactions occurred in 8 per cent. of their patients and that toxic reactions were twice as common in women as in men, but none had occurred in children. Heyworth and Helm (1960) stated that thirty neurotoxic reactions occurred in 148 of their patients and the incidence was one in five under the age of 50 and one in three over the age of 50. Riches (1954a) stated that, of 150 patients treated with streptomycin 36 per cent. complained of toxic symptoms on the day of the injection and that, in 8 per cent. of a total of nineteen patients who had had severe reactions, the symptoms were worse with exercise.

A case of an adverse allergic reaction to streptomycin is described below.

Case Report

A male Greek-Cypriot, aged 28 years, was seen in the venereal diseases department on October 28, 1963, complaining of urethral discharge of 4 days' duration which had commenced 10 days after sexual intercourse with a stranger. There were no other symptoms. He had previously been treated for attacks of gonorrhoea in 1959 and 1961 with injections of penicillin and Actinospectacin respectively with no ill effect; 3 months before the second attack of gonorrhoea (in 1961) he had been given a 5-day course of sulphadimidine tablets with no ill effect, for a purulent balanoposthitis caused by an attack of herpes genitalis.

Examination.—He was found to have a purulent urethral discharge associated with a cloudy urine containing threads in both specimens of the two-glass test. A urethral smear stained by Gram's method failed to demonstrate the gonococcus, but many pus cells were present. A saline suspension preparation failed to demonstrate *Trichomonas vaginalis*. Standard tests for syphilis (S.T.S.) on blood serum were also negative. He was thought to have a non-gonococcal urethritis (N.G.U.).

Treatment.—He was given an injection of 1 g. streptomycin followed by sulphadimidine tablets to be taken 1 g. four times a day for 5 days.

Progress.—The next day he returned complaining of a rash which had broken out on his lower lip and right arm, after a period of irritation which had commenced one hour after the streptomycin injection, but before he had taken any sulphadimidine. The urethral discharge had also become worse, otherwise there were no other presenting symptoms.

Examination.—He had a bullous eruption on the left side of the lower lip 1·5 cm. in diameter (Fig. 1) and an erythematous macular eruption 5·5 cm. in diameter on the medial side of the right arm close to the elbow (Fig. 2).

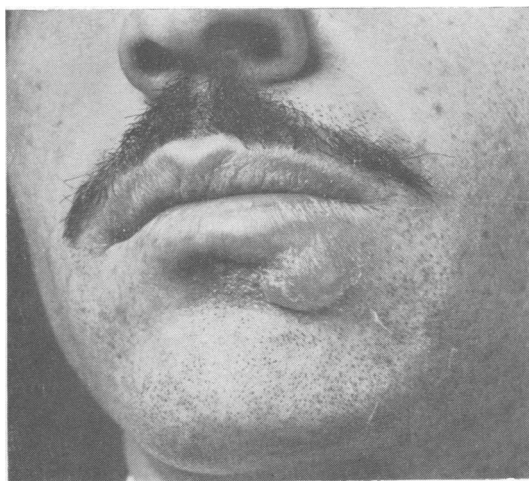


FIG. 1.—Bullous eruption on lower lip.



FIG. 2.—Macular eruption on medial border of right arm.

A second urethral smear stained by Gram's method demonstrated the gonococcus.

Treatment.—He was given an injection of 1 ml. (10 mg.) Piriton, followed by a long-acting oral preparation of Piriton doulets to be taken twice a day and local applications of lotio Caladryl to the areas affected by the rash. For the gonorrhoea he was given oral tetracycline 500 mg. to be taken four times a day for 2 days.

Progress.—He returned 2 days later with considerable improvement in the rash, but he had developed symptoms and signs of a balanoposthitis, although the urethral discharge was much less. Both urine specimens in the two-glass test contained threads, but no sugar was detected. He was treated with subpreputial irrigations of hydrogen peroxide and local applications of Propamide cream twice a day; 4 days later the balanoposthitis had improved and there was no urethral discharge, although threads could be detected in both urine specimens of the two-glass test. After 2 weeks he returned with a recurrence of the urethral discharge, but there had been no further sexual intercourse. The discharge was found to be mucopurulent with threads in the first urine specimen of the two-glass test. A urethral smear stained by Gram's method demonstrated pus cells only. A saline suspension preparation failed to demonstrate *Trichomonas vaginalis*. A 5-day course of oral tetracycline 250 mg. four times a day was prescribed, after which the patient defaulted.

Discussion

Streptomycin is a complex chemical substance ($C_{21}H_{39}N_7O_{12}$) composed of an amine-substituted disaccharide (streptobiosamine) that is linked to a 1,3-diguanidino—2, 4, 5, 6 tetrahydrocyclohexane (streptidine). Keil and Trosow (1948) thought that the streptidine portion of the molecule was responsible for allergic reactions, since this could be split off by acid hydrolysis as a result of enzymatic action in the skin. Streptidine also contains two guanidine groups, and guanidine derivatives are known to cause allergic skin reactions. In this respect it is of interest to note that Chakravarty and Sircar (1961) described irritation at the site of the injection as the commonest allergic manifestation to this drug. Sandler (1955), however, thought that allergic skin reactions were due to hypersensitivity to the sulphate radicle, since patients were better able to tolerate the calcium chloride complex.

The time of onset of reactions to streptomycin is variable. Riches (1954b) stated that reactions usually occurred 1 to 3 hours after the injection and corresponded with the peak level of streptomycin in the blood. Sandler (1955), however, stated that true hypersensitivity developed after an average time of 14 days of continuous treatment. Smith and Zirk (1961) found that most allergic reactions occurred

within 5 weeks of continuous treatment, but some were delayed up to 6 months. Kalinowski (1960) stated that more reactions occurred between the fourth and sixth week, but they may occur after the first dose or after 6 months of continuous treatment.

The treatment of adverse reactions to streptomycin depends on whether they are allergic or toxic in origin. In both instances, however, further administration of the drug should be stopped and therapy to counteract the effects of the reaction should be given at once. Allergic reactions can be treated with antihistamines or corticosteroids, both systemically and locally. Cases of anaphylaxis will also require routine treatment for shock. Once the reaction has subsided, however, the drug can be given again with careful supervision under an antihistamine or corticosteroid "cover", or after a period of "desensitization" in which increasing doses of the drug are given over a prolonged time. Smith and Zirk (1961) recommended an initial dose of 0.01 g., followed by daily increments of this amount until 0.1 g. had been given and further daily increments of this dose until 1 g. had been given. They also advised giving at the same time 20 mg. prednisolone or an equivalent steroid daily as a precaution. Toxic reactions are more difficult to treat, but in the majority of cases they can be overcome by reduction in dosage.

Prevention by means of skin tests or the use of a "test dose" is another method of dealing with this problem. Chakravarty and Sircar (1961) used a patch test of 1.0 per cent. solution of streptomycin sulphate on the skin and found that 11.8 per cent. of their patients gave a positive result, of which 0.8 per cent. were "false positive", out of 10.9 per cent. of patients who later developed allergy. Smith and Zirk (1961), however, thought that the use of Bencard patch tests, applied for 48 hours and "prick tests" read after 10 to 15 minutes were of no value and that a "test dose" was a much better method of assessing sensitivity. Sandler (1955) also thought that a "test dose" of 0.5 g. streptomycin given by intramuscular injection was the most reliable method of assessing sensitivity and this was supported by Aamodt (1959), who found that an intracutaneous "test dose" of 0.025 g. of streptomycin sulphate read after 11 hours gave accurate results.

Summary

A case of an allergic reaction to streptomycin, presenting as a bullous and macular skin eruption, is described.

The literature on the incidence and types of adverse reactions to streptomycin, together with their treatment and prevention, is reviewed.

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Sensibilisation à la streptomycine

RÉSUMÉ

On présente un cas de réaction allergique à la streptomycine caractérisé par une éruption maculaire et bulleuse.

On passe en revue la littérature existante sur l'incidence des différents types de réactions défavorables à la streptomycine, en même temps que leur traitement et leur prévention.